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CASE REPORT

Atypical femoral fracture after long-term alendronate treatment: Report of a case evidenced with magnetic resonance imaging

Chih-Ming Kao [a], Peng-Ju Huang [b,c], Chung-Hwan Chen [a,b,d], Shu-Jung Chen [a], Yuh-Min Cheng [a,b,*]

[a] *Department of Orthopaedics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[b] *Department of Orthopaedics, Faculty of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Department of Orthopaedics, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[d] *Graduate Institute of Medicine, College of Medicine, Orthopaedic Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan*

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Abstract Postmenopausal osteoporosis is commonly treated with alendronate, one of the bisphosphonates used for the prevention and treatment of osteoporotic fractures. However, the correlation between atypical femoral fractures and long-term bisphosphonate therapy has not been clearly identified. We report here the case of a 69-year-old woman with postmenopausal osteoporosis who presented with an atypical femoral subtrochanteric fracture on magnetic resonance imaging (MRI) confirmation after having received alendronate therapy for about 3 years. The fracture united after refixation and after administration of alendronate was stopped. Several published reports were reviewed, and some clinical characteristics of this atraumatic fracture were revealed, including the clinical symptoms of thigh pain, stress reaction or stress fracture, and transverse fracture with unicortical beak in an area of cortical hypertrophy. In addition to a regular radiographic survey, MRI, which may provide early information, and bone biopsy for pathologic analysis may be used as tools for early detection and final diagnosis. Once an insufficiency fracture is suspected or proved to be related to bisphosphonate, the withholding of bisphosphonate should be highly recommended to enhance

* Corresponding author. Department of Orthopaedics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, 100 Tzu-You First Road, Kaohsiung City, Taiwan.
E-mail address: 0710058@kmhk.kmu.edu.tw (Y.-M. Cheng).

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fracture healing. Prophylactic fixation should be considered if fracture healing is not good or if the patient cannot tolerate protection of weight-bearing.

Introduction

Alendronate, one of the bisphosphonates, is a potent inhibitor of bone resorption, and is also prescribed as a first-line therapy for postmenopausal osteoporosis [1]. In addition, osteoporotic fractures may be prevented with alendronate. Both clinically important as well as statistically significant reductions in vertebral, nonvertebral, hip, and wrist fractures have been observed with the use of alendronate at 10 mg/d for secondary prevention [2]. There is no consensus on the duration of treatment [3]. However, in recent years, reports on low-energy femoral subtrochanteric or shaft fracture after long-term bisphosphonate use have been published [4—11], although no significant increase in risk associated with bisphosphonate use has been found in large-scale studies [12,13]. In this article, we present the case of a 69-year-old woman with a history of left atypical femoral fracture after long-term alendronate therapy; the fracture was confirmed by magnetic resonance imaging (MRI).

Case report

Osteoporosis was diagnosed in a 55-year-old woman based on a lumbar bone mineral density (BMD) survey (T-score −3.39) at L2—L4, using Norland 36R dual-energy X-ray absorptiometry (Fort Atkinson, WI, USA) in September 1995. She had a 20-year history of bilateral knee osteoarthritis, as well as a history of postmenopausal syndrome of about 9 years. According to her medical records, she had histories of glucosamine sulphate therapy for osteoarthritis and medroxyprogesterone therapy for postmenopausal syndrome. She took a calcium supplement, due to lack of reimbursement by health insurance.

In 2006, when she was 66 years old, she started taking Fosamax (70 mg alendronate acid) and a calcium supplement once weekly. About 2 years after starting alendronate use, she complained of left lateral thigh pain while walking. After serial examinations, lesions at the hip joint and lumbar spine as a cause of lateral thigh pain were excluded. Radiography of the hip showed thickening of the cortex with a cleft at the lateral cortex, which was suspected to be an insufficiency fracture of the left proximal femoral shaft with callus formation. An MRI study also confirmed the diagnosis of insufficiency fracture with no other pathology (Fig. 1). She had no other risk factor for pathologic fracture, including cigarette smoking, corticosteroid usage, or history of malignancy. Non-weight-bearing was suggested at that time, but the patient was not able to do this.

She visited the emergency department due to a sudden onset of severe left hip pain with deformity while standing up from a chair, about 3 years after the beginning of alendronate use. No history of trauma or muscle weakness was noted at that time. In the emergency department, a radiograph of the left hip showed a left proximal femoral transverse fracture in the subtrochanteric area with displacement, which was compatible with a complete fracture of the previous stress fracture (Fig. 2). No other obvious bone lesion, including malignant change, was noted. An intramedullary nail with locking screws was used for fixation of the fracture. At the same time, a bone biopsy was taken for pathologic examination, revealing dead bone trabeculae with hemorrhage in the marrow spaces, which further excluded the possibility of malignancy. The patient was discharged without any complications. Alendronate

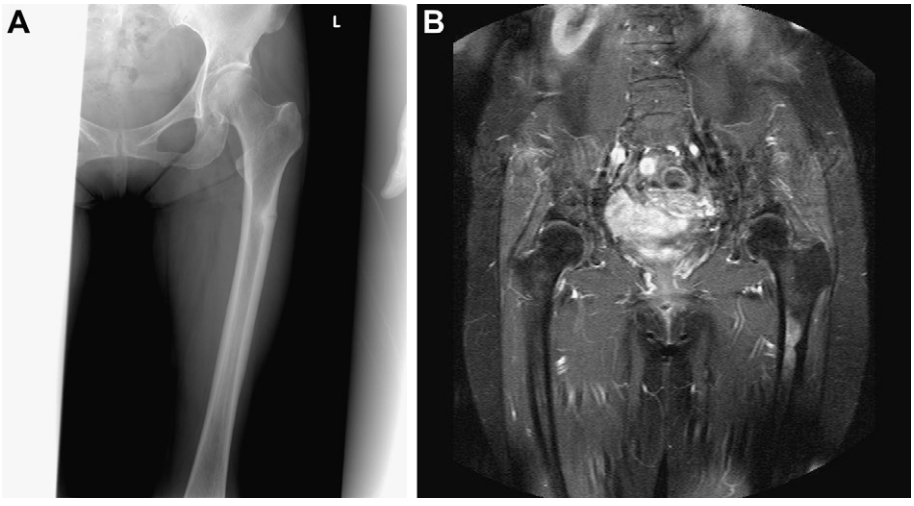

Figure 1. (A) Radiograph of the left proximal femoral shaft showing a radiolucent line and focal thickening of the lateral cortex. (B) Magnetic resonance imaging reveals the same finding, which indicates stress fracture. The subsequent femur insufficiency fracture occurred in the same area.

Figure 2. Radiograph demonstrating a left subtrochanteric fracture with displacement.

was withheld because of the suspicion of a possible bisphosphonate-related stress fracture.

At the third month of follow-up, non-healing of the left femur subtrochanteric fracture and a broken intramedullary nail were noted (Fig. 3). Internal fixation was again performed, and the fracture united 3 months after the second operation.

Discussion

Currently, bisphosphonates are the most popular anti-resorptive agents available to treat osteoclast-mediated bone resorption disease, including osteoporosis, Paget's disease, and metastatic bone disease [1]. Alendronate was the first drug to be approved by the US Food and Drug Administration in 1995, and it was reported to be well tolerated over a 10-year period [14]. When comparing daily alendronate with placebo, BMD of the lumbar spine continuously increased with alendronate use, and no association between prolonged use of alendronate and an excess risk of fracture was found [14].

However, recent studies suggest that long-term bisphosphonate use may be related to low-energy subtrochanteric and femoral shaft fractures [4—8,10,11,15—17]. There have been a few cases reported in Asian patients. In one case report, a 72-year-old woman who had been taking alendronate and calcium supplement therapy for 7 years suffered a displaced transverse subtrochanteric femoral fracture, and was operated on to insert a long gamma nail [18]. Similar to our case, she suffered from thigh pain for 1 year before the fracture, and about 3 months postoperatively the radiographs also showed signs of poor healing of the fracture. Very few studies have included an MRI study that has confirmed the diagnosis of insufficiency fracture. In our study, we performed an MRI examination before the complete fracture of the subtrochanteric region, which confirmed the diagnosis of insufficiency fracture and excluded other pathologies.

In a study from Singapore, the researchers reviewed 17 patients who had undergone alendronate therapy for an average of 4.8 years, and observed the typical fracture configuration in all patients; this included (1) cortical thickening of the lateral (tension) side of the subtrochanteric region, (2) transverse fracture, and (3) a medial cortical spike [6]. In another study, patients with femoral shaft fractures who were taking alendronate were reviewed, demonstrating an association between alendronate therapy

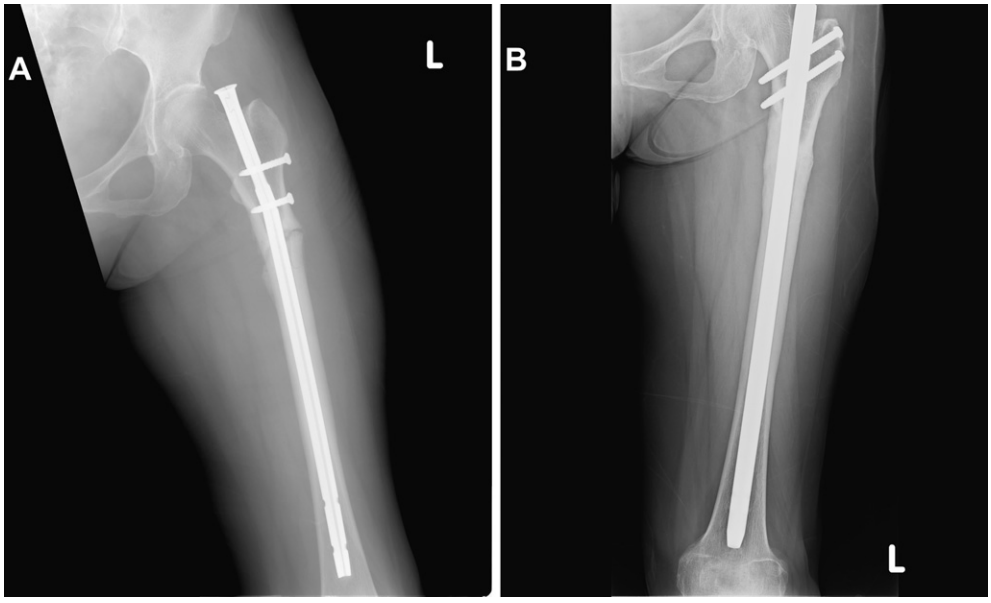

Figure 3. (A) Subtrochanteric fracture of the left femur with intramedullary nail fixation, showing poor healing with a broken nail. (B) Good union was shown 3 months after the second operation.

and the specific pattern of low-energy femoral shaft fracture [7]. Similar results were characterized by a transverse fracture with a unicortical beak in an area of cortical hypertrophy. The same fracture pattern was noted in our case. These specific fracture patterns may result from the effect of a stress fracture, the impaired repair of which may be highly suspected to be related to prolonged alendronate use.

Koh et al. demonstrated the cortical stress reactions associated with prolonged antiresorptive therapy by reviewing 32 patients who were receiving alendronate therapy and who suffered from low-energy hip fracture [19]. From the results, these authors concluded that, in the presence of thigh pain, the "dreaded black line" on radiographs revealed an increased risk for complete stress fracture. In our case, the radiograph of the left proximal femoral shaft before subtrochanteric fracture showed a radiolucent line and focal thickening of the cortex, which indicated a stress fracture. The stress reaction characterized by computed tomography and MRI [6] was reported, and the same image was also noted on our patient's MRI before the complete fracture. The stress reaction detected by MRI or radiography can be used as the portent of a low-energy fracture related to alendronate. In particular, MRI may be used in symptomatic patients taking alendronate for the early detection and prevention of a fracture.

It seems that some specific patterns of insufficiency fracture can be correlated with long-term bisphosphonate therapy in Asian populations. The clinical symptom of thigh pain of other than spinal or hip origin, and the stress reaction or stress fracture on MRI or radiography, may be used for early detection of these insufficiency fractures. Even though a causal relationship between alendronate use and femoral insufficiency fracture has not yet been established [12,13], we have to keep in mind the possible association between alendronate and femoral insufficiency fracture if the thigh pain cannot be identified as being of hip or spinal origin. It is reasonable at that time to switch from bisphosphonate to an alternative therapy for osteoporosis.

Once the insufficiency fracture is proved or suspected to be related to bisphosphonate, stopping bisphosphonate should be highly recommended to enhance fracture healing. Prophylactic fixation should be considered if fracture healing is not good or the patient cannot tolerate protection of weight-bearing. In conclusion, femoral subtrochanteric insufficiency fracture should be kept in mind when a patient has taken a bisphosphonate for a long time and complains of lateral thigh pain without an obvious hip or spinal lesion. An MRI is of value in the diagnosis of such patients.

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